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REVIEW ARTICLE

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Proven *Aspergillus flavus* pulmonary aspergillosis in a COVID-19 patient: A case report and review of the literature

Mohammadreza Salehi[1] | Nasim Khajavirad[2] | Arash Seifi[1] | Faeze Salahshour[3] | Behnaz Jahanbin[4] | Hossein Kazemizadeh[5] | Sayed Jamal Hashemi[6] | Seyed Ali Dehghan Manshadi[1] | Mohammad Kord[6] | Paul E. Verweij[7] | Sadegh Khodavaisy[6]

[1]Department of Infectious Diseases and Tropical Medicine, Imam Khomeini Hospital complex, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Internal Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Radiology, School of Medicine, Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Imam Khomeini Hospital complex, Tehran University of Medical Sciences, Tehran, Iran

[4]Pathology Department, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

[5]Advanced Thoracic Research Center, Occupational Sleep Research Center, Tehran University of Medical Sciences, Tehran, Iran

[6]Department of Medical Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

[7]Department of Medical Microbiology and Center of Expertise in Mycology Radboudumc/CWZ, Radboud University Medical Centre, Nijmegen, The Netherlands

Correspondence
Sadegh Khodavaisy, Department of Medical Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Email: sadegh_7392008@yahoo.com

Abstract

Severe COVID-19 patients complicated with aspergillosis are increasingly reported. We present a histopathological proven case of fatal COVID-19–associated pulmonary aspergillosis (CAPA), due to *Aspergillus flavus*. This report and existing published literature indicate diagnostic challenges and poor outcomes of CAPA in ICU patients.

KEYWORDS
Aspergillosis, COVID-19, Immunocompetent

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been sweeping across the globe. Like severe influenza pneumonia, COVID-19 is associated with acute respiratory distress syndrome (ARDS), which might be considered a risk of fungal colonisation and infection of the respiratory tract.[1,2] Mortality in severe COVID-19 cases is significant compared with non-severe infection cases due to the higher co-infection rate.[3] Unlike bacterial co-infections, the risk of fungal co-infections, including oropharyngeal candidiasis, invasive aspergillosis (IA), endemic mycoses, mucormycosis and fusariosis is notable in patients with severe COVID-19, despite the absence of classical well-defined host factors.[4-12] Possible explanations for the development of fungal co-infections include immune paralysis caused by COVID-19 infection–induced ARDS, diffuse alveolar damage with severe inflammatory exudation and lymphopenia.[13,14] Preliminary reports showed 19-33% of severe COVID-19–associated pulmonary aspergillosis (CAPA) in ICU patients.[15,16] Research findings strongly suggest that mechanically ventilated COVID-19 patients with longer duration of hospital admission should be systematically screened for *Aspergillus* infections.[15] Here, we describe CAPA in an immunocompetent patient and review the available literature on the subject.

2 | CASE REPORT

A 70-year-old man with a history of recent hospital admission due to SARS-CoV-2 infection with the diagnosis of exacerbation of viral pneumonia that was had been referred to Imam Khomeini Hospital complex Tehran, Iran. Imam Khomeini Hospital complex is the largest referral centre in the country, admitted 25,410 patients in 2020 alone. Time course of the patient is detailed in Figure 1. In

the previous hospitalisation, COVID-19 infection was confirmed by positive nasopharyngeal PCR and with more than 50% field involvement of both lungs on chest CT scan. At the first admission, he had received hydroxychloroquine 200 mg/PO/BID for 5 days, interferon beta-1 A/SC/every other day for 5 doses and dexamethasone 8 mg/IV/ daily according to the country guideline and had been discharged from the hospital after 12 days with a partial clinical recovery. However, after 3 days he was re-admitted with exacerbation of respiratory symptoms. On admission, his respiratory rate was 28 /min and Spo2 in room air was 80%. The patient's laboratory data showed lymphopenia (216/mL) and elevated inflammatory markers (ESR: 30 mm/1hr, CRP: 40 mg/L, ferritin: 3,000 ng/mL, lactic acid dehydrogenase: 440 U/L and marked elevated D-dimer: 2,572 ng/mL). Other laboratory results included WBC: 7,200/mL, PMN: 95.5%, Hb: 16 gr/dL, PLT: 176,000/mL and creatinine: 1.1 mg/dL. SARS-CoV-2 PCR test was still positive at the time of his re-admission. Chest CT scan (Figure 2A) revealed multilobar peripheral ground-glass opacities compatible with COVID-19 pneumonia (>50% involvement). Evaluation for heart diseases was negative (normal echocardiography). According to the progression

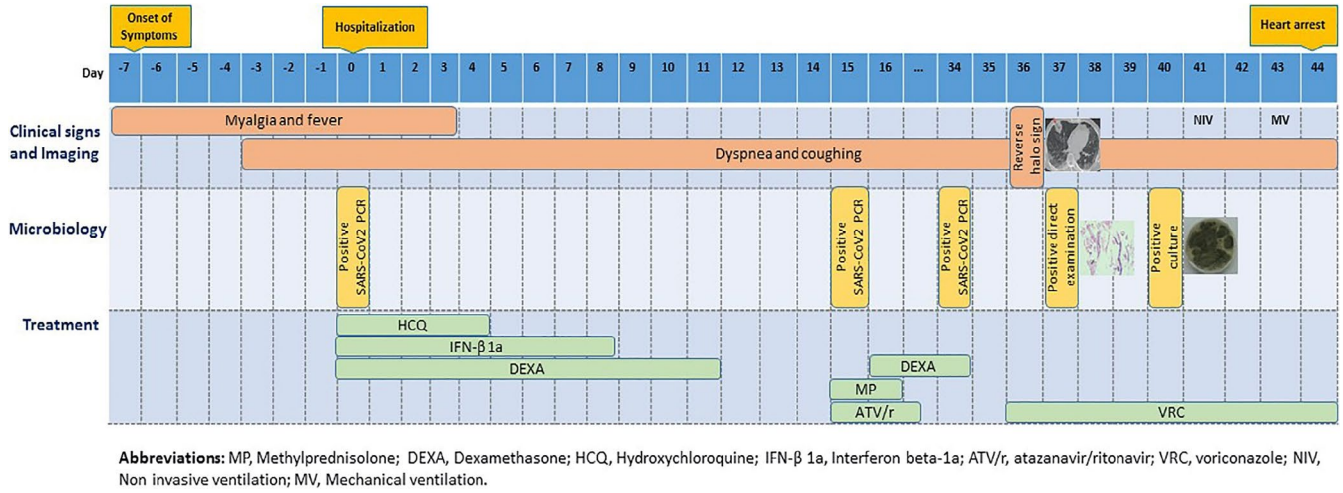

FIGURE 1 Timeline of the patient with COVID-19–associated pulmonary aspergillosis

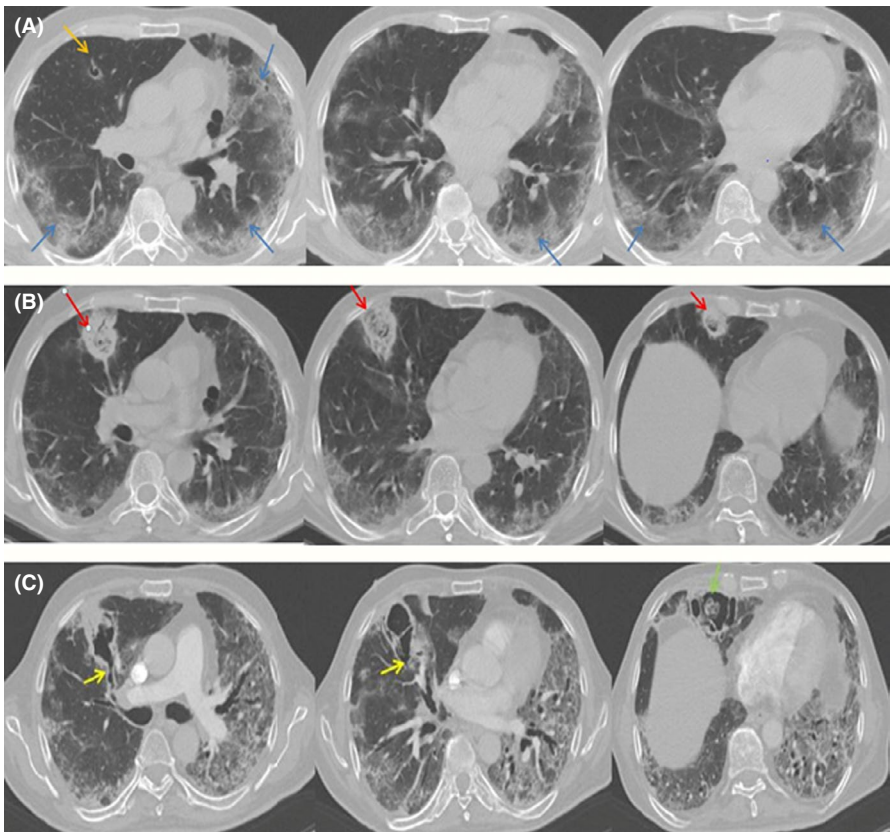

FIGURE 2 A, Contrast-enhanced computed tomography chest showing multi-lobar peripheral ground-glass opacities; B, the reduced ground-glass opacities and three new foci of peripheral wedge-shaped air-space opacities with reverse halo developed in the right middle lobe; C, the yellow arrows depict the foci of bronchial wall defects. The green arrow shows sloughed debris mimicking invasive aspergillosis

of lung involvement due to the SARS-CoV-2 infection, the patient was treated with high-dose methylprednisolone 250 mg/daily/IV for 3 days followed by dexamethasone 4 mg/IV/TID, atazanavir/ritonavir/PO/daily and supportive care. With the start of treatment, the patient's condition slightly improved, respiratory distress decreased and SpO2 reached 88% in room air, but in the second week of hospitalisation, the recovery process was not significant. In the third week of hospitalisation due to not achieving the desired therapeutic result, especially in the respiratory symptoms and persistence of high inflammatory markers, the patient underwent a new diagnostic evaluation. SARS-CoV-2 PCR test was reported positive again. A second CT scan showed reduction in ground-glass opacities and three new foci of peripheral wedge-shaped air-space opacities with reverse halo in the right middle lobe (Figure 2B). Sputum samples for acid-fast bacilli were negative. Because of likely/plausible fungal infection, voriconazole (6 mg/kg/BID day one followed by 4 mg/kg/BID) was started and the corticosteroid dose (dexamethasone 4 mg/IV/ daily) was reduced. Tissue obtained through CT-guided biopsy of a peripheral lung lesion showed septate hyphae consistent with *Aspergillus*. Culture of the biopsy samples showed growth of green, powdery surface colonies suspected for *Aspergillus* spp. (Figure 3). Molecular identification was performed based on beta-tubulin gene sequence [17] and identified as *Aspergillus flavus*. Despite antifungal therapy for 5 days, respiratory failure progressed and he went on non-invasive ventilation support. Follow-up CT scan showed that the opacities had evolved into irregular cavities, one of which contained sloughed debris mimicking a fungus ball and two cavities connected with bronchial lumen via bronchial wall defects (Figure 2C). After 48 hours, the patient was intubated on mechanical ventilation due to progressive respiratory failure, while continuing dexamethasone, voriconazole, sofosbuvir/daclatasvir and meropenem therapy. Unfortunately, the patient died after 12 hours with cardiac arrest. An autopsy was not performed.

2.1 | Literature review

The English literature was reviewed for published CAPA cases using search terms “corona”, “COVID-19”, “aspergillosis”, “CAPA” and “fungal”. A total of 175 CAPA cases were found and details are presented in Table 1. Although variable case definitions were used, only 7 (4%) cases were classified as proven CAPA.

3 | DISCUSSION

Although secondary bacterial and viral infections are reported at low frequency in COVID-19 patients, high frequencies of CAPA cases are published in association with COVID-19 in the ICU. Case series from the Netherlands, Germany and France reported CAPA 19%, 26% and 33% of patients with severe COVID-19 pneumonia, respectively.[5] Although lower rates were reported from Switzerland (3.8%) and China (7%).[18,19] A major challenge remains diagnosing CAPA as the performance of diagnostic *Aspergillus* biomarkers remains suboptimal. Serum galactomannan (GM) detection is commonly negative even in patients with proven CAPA.[20] In our reviewed cases, serum GM was performed in 73 of 183 CAPA patients (39.8%), while GM was detected in only 19 (26%) patients (Table 1). Bronchoscopy with bronchoalveolar lavage (BAL) remains the preferred diagnostic procedure to diagnose CAPA, and GM was detected in 83 of 105 (79%) CAPA patients who underwent bronchoscopy.[21] However, bronchoscopy with BAL involves an

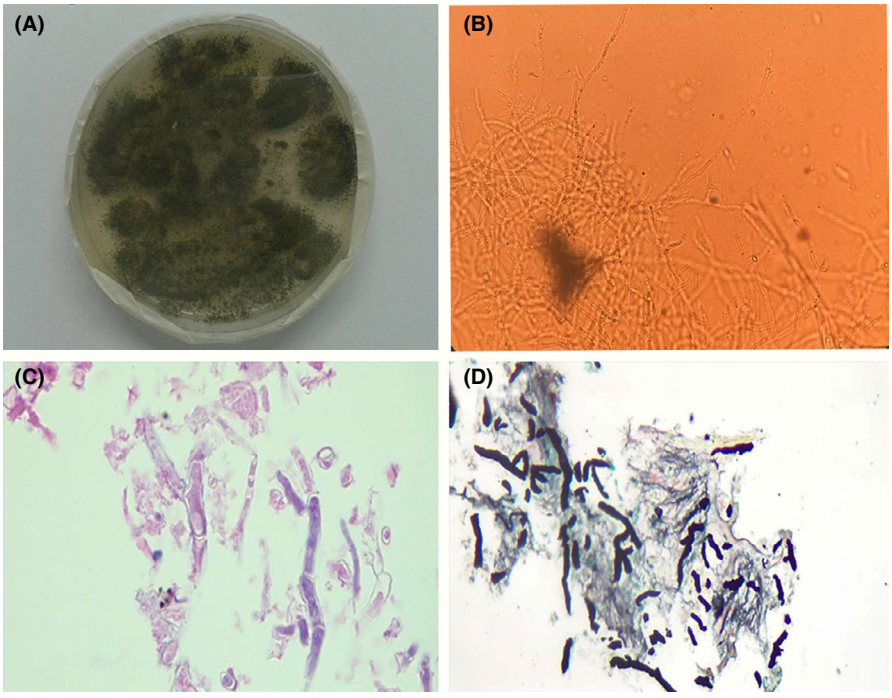

FIGURE 3 A, Culture on Sabouraud dextrose agar produced green, powdery surface colonies; B, Direct examination of the sample with KOH 10% show hyaline and septated hyphae (×400); C H&E staining show branched and septated hyphae with acute angle hyphae [100X objective]; D, Gomori's methenamine silver (GMS) staining highlights acute angle hyphae [40X objective]

TABLE 1 Summary of previously reported cases of *Aspergillus* infection in COVID-19 patients

Authors/ References	Country	Number of patients	Mean age (SD)	Sex Malen (%)	BAL | Serum GM*positive/total (%)	Mechanical ventilationn (%)	Culture / PCRn (%)	Aspergillus species/ Respirator samples (n)	Antifungal therapyn (%)	Outcome (mortality) n (%)
Bartoletti *et al* [6]	Italy	30	63	24 (80)	30/30 (100) | 0/1 (0)	30 (100)	19 (63) / 20 (67)	*A fumigatus* (15), *A niger* (3), *A flavus* (1) / ND	VRC 13 (43)	13 (44%)[a]
White *et al* [25]	United Kingdom	25	ND	ND	17/19 (89.5) | 1/4 (25)	18 (72)	11 (44) / 16 (64)	*A fumigatus* (10) / NBL (10)	VRC 9 (36), CSP + VRC 2 (8), AMB 2 (12), VRC + AMB 2 (8), FLU 1 (4), VRC + FLU 1 (4), ANI + AMB 1 (4)	13 (52)
Marr *et al* [35]	USA	20	65.5	9 (45)	1/1 (100) | 4/16 (25)	ND	17 (85) / ND	*A fumigatus* (10), *A niger* (2), *A terreus* (1), *A fumigatus + A niger* (2), *Aspergillus spp.* (2)/ ND	VRC + PSO 1 (5), AMB 1 (5)	3 (15)
Dupont *et al* [4]	France	19	68.4	16 (84.2)	5/9 (55.6) | ND	18 (94.7)	16 (84.2) / ND	*A fumigatus* (14), *A calidoustus* (1), *A niger* (1) / BAL (8), TA (4), BA (6)	VRC 8 (42.1) VRC + CSP 1 (5.3)	7 (36.8)
Falces-Romero *et al* [36]	Spain	10	67.1	8 (80)	2/2 (100) | 1/2 (50)	7 (70)	10 (100) / ND	*A fumigatus* (9), *A nidulans* (1) / BA (10)	VRC 2(20), AMB 1(10), VRC + CSP 1(10), AMB + ISA 1(10), AMB + VRC 1(10), AMB + ANI 1(10), MICA + AMB+ISA + VRC 1(10)	7 (70)
Alanio *et al* [15]	France	9	62.8	6 (66.7)	1/7 (14.3) | 0/8 (0)	9 (100)	7 (77.8) / 4 (44.4)	*A fumigatus* (7) / BAL (5), TA (2)	VRC 1 (11.1) CSP 1 (11.1)	4 (44.4)
Wang *et al* [18]	China	8	73	8 (100)	ND	4 (50)	8 (100) / ND	*A fumigatus* (8) / BAL (4), Sputum (4)	ND	ND
Rutsaert *et al* [20]	Belgium	7	66.6	7 (100)	5/6 (83.3) | 0/6 (0)	7 (100)	6 (85.7) / ND	*A fumigatus* (5), *A flavus* (1) / BAL (6), TA (1)	VRC + ISA 2 (28.6), VRC 4 (57.1)	4 (57.1)
Flikweert *et al* [24]	Netherlands	7	73	5 (71.4)	6/7 (85.7) | ND	7 (100)	2 (28.6) / ND	*A fumigatus* (2) / BAL (2)	VRC + ANI 6 (85.7)	7 (100)
van Arkel *et al* [37]	Netherlands	6	63.8	6 (100)	3/3 (100) | 0/3 (0)	ND	5 (83.3) / ND	*A fumigatus* (4), *Aspergillus* spp. (1) / TA (2), BAL (3), Sputum (1)	VRC 5 (83.3), AMB 1 (16.7)	4 (66.7)
Koehler *et al* [16]	Germany	5	62.6	3 (60)	3/3 (100) | 1/5 (20)	5 (100)	4 (80) / 4 (80)	*A fumigatus* (4) / BAL (2), TA (2)	VRC 2 (28.6), AMB 2 (28.6), CSP 2 (28.6), ISA 1(14.3)	3 (60)
Nasir *et al* [5]	Pakistan	5	69	3 (60)	ND | 0/5 (0)	2 (40)	5 (100) / ND	*A flavus* (3), *A niger* (1), *A flavus/A fumigatus* (1) / ND	VRC 3 (33.3), AMB 2 (22.2)	3 (60)
Sarrazyn *et al* [38]	Belgium	4	75	3 (75)	4/4 (100) | ND	4 (100)	4 (100) / 2 (50)	*Aspergillus* spp. (4) / ND	VRC 1 (25), AMB + VRC 2 (50)	ND

(Continues)

TABLE 1 (Continued)

Authors/ References	Country	Number of patients	Mean age (SD)	Sex Malen (%)	BAL | Serum GM*positive/total (%)	Mechanical ventilationn (%)	Culture / PCRn (%)	Aspergillus species/ Respirator samples (n)	Antifungal therapyn (%)	Outcome (mortality) n (%)
Mitaka *et al* [39]	USA	4	78.7	4 (100)	ND |1/4 (25)	4 (100)	4 (100) / ND	*A fumigatus* (4) / ND	VRC 3 (75), CSP 1 (25)	3 (75)
Lahmer *et al* [40]	Germany	2	75	2 (100)	2/2 (100) | 1/2 (50)	2 (100)	2 (100) / ND	*A fumigatus* (2) / BAL (2)	AMB 2 (100)	2 (100)
Lescure *et al* [41]	France	1	80	1 (100)	ND	1 (100)	1 (100) / ND	*A flavus* / TA	VRC, ISA	1 (100)
Blaize *et al* [42]	France	1	74	1 (100)	0/1 (0) | ND	1 (100)	1 (100) / 1 (100)	*A fumigatus* / TA	ND	1 (100)
Antinori *et al* [43]	Italy	1	73	1 (100)	ND | 1/1 (100)	1 (100)	1 (100) / ND	*A fumigatus* / BAL	AMB	1 (100)
Prattes *et al* [44]	Austria	1	70	1 (100)	ND | 0/1 (0)	1 (100)	1 (100) / ND	*A fumigatus* / TA	VRC	1 (100)
Meijer *et al* [7]	Netherlands	1	74	0 (0)	1/1 (100) | 0/1	1 (100)	1 (100) / ND	*A fumigatus* / TA	VRC + CSP	1 (100)
Santana *et al* [45]	Brazil	1	71	1 (100)	0/1 (0) | 1/1 (100)	1 (100)	1 (100) / 1 (100)	*A penicillioides* / Autopsy	ND	1 (100)
Sharma *et al* [46]	Australia	1	66	0 (0)	ND	1 (100)	1 (100) / ND	*A fumigatus* / TA	VRC	0 (0)
Wu *et al* [47]	China	1	46	1 (100)	ND	ND	1 (100) / ND	*A fumigatus* / Sputum	VRC	0 (0)
Schein *et al* [48]	France	1	87	0 (0)	1/1 (100) | 1/1 (100)	ND	0 / 1 (100)	ND	VRC	1 (100)
Nasri *et al* [49]	Iran	1	42	0 (0)	ND | 1/1 (100)	1 (100)	ND / ND	ND	AMB	1 (100)
Mohamed *et al* [9]	Ireland	1	66	1 (100)	ND | 1/1 (100)	1 (100)	1 (100) / ND	*A fumigatus* / TA	AMB	1 (100)
Ghelfenstein *et al* [50]	France	1	56	1 (100)	ND | 0/1 (0)	1(100)	1 (100) / ND	*A fumigatus* / TA	ND	1 (100)
Fernandez *et al* [51]	Argentina	1	85	1 (100)	ND | 1/1 (100)	1 (100)	1 (100) / ND	*A flavus* / TA	VRC	1 (100)
Machado *et al*[29]	Spain	8	65	6 (75)	2/8 (25) | 4/8 (50)	8 (100)	8 (100) / 1 (100)	*A fumigatus* (5), *A fumigatus* + *A awamori* + *A terreus*(1), *A lentulus*(1), *A citrinoterreus*(1) / BA (5), BAL (2), TA (1)	AMB 2 (25), VRC 2 (25), ISA 4 (50)	8 (100) [a]

(Continues)

TABLE 1 (Continued)

Authors/ References	Country	Number of patients	Mean age (SD)	Sex Malen (%)	BAL | Serum GM*positive/total (%)	Mechanical ventilationn (%)	Culture / PCRn (%)	Aspergillus species/ Respirator samples (n)	Antifungal therapyn (%)	Outcome (mortality) n (%)
Our study	Iran	1	70	1 (100)	ND | ND	1 (100)	1 (100) / 1 (100)	*A flavus* / Biopsy	VRC	1 (100)
Total	-	183	68.5 (±9.6)	120 (65)	83/105 (79) | 19/73 (26)	135 (73.7)	140 (76.5) / 51 (27.8)	*A fumigatus*(107), *A flavus* (8), *A niger* (7), *A nidulans* (1), *A terreus* (1), *A penicillioides* (1), *A calidoustus* (1), *A lentulus* (1), *A citrinoterreus* (1), *Aspergillus* spp. (7) Mix Aspergillus spp. (4)/ BAL (34), TA (20), BA (21), NBL (10), Sputum (6), Biopsy (1), Autopsy (1)	VRC 60 (32.7), AMB 16 (8.7), CSP 5 (2.6), FLU 1 (0.5), ISA 5 (2.7), Antifungal combination 24 (13.7)	93 (50.8)

Abbreviations: AMB, amphotericin B; ANI, anidulafungin; BA, bronchial aspirate; BAL, bronchoalveolar lavage; CSP, caspofungin; FLU, fluconazole; GM, galactomannan; ISA, isavuconazole; MICA, micafungin; NBL: non-directed bronchial lavage; ND, not determined; PCR, polymerase chain reaction; PSO, posaconazole; SD, standard deviation; TA, tracheal aspirate; VRC, voriconazole.

[a]Authors indicated CAPA-related mortality.

*Galactomannan values interpreted according to EORTC/MSGERC.[52] EORTC/MSGERC denotes European Organization for Research and Treatment of Cancer/ Mycoses Study Group Education and Research Consortium.

aerosol-producing procedure with contamination risk for healthcare workers. Although bronchoscopy is recommended to diagnose secondary infection in severe COVID-19 cases,[22] many centres rely on bronchial aspirate or sputum to diagnose CAPA.[2] However, recovery of *Aspergillus* from these specimens may reflect upper respiratory tract colonisation rather than invasive infection.[23] Furthermore, there is conflicting evidence that supports both colonisation and invasive infection in *Aspergillus*-positive COVID-19 patients. On the one hand, COVID-19 patients with evidence for *Aspergillus* have survived without antifungal therapy, which suggests that a positive culture or GM represents colonisation.[15] Furthermore, post-mortem CT-guided lung biopsies showed no evidence of IA, even in patients with positive BAL-GM.[24] However, on the other hand several case series have shown a higher mortality in ICU patients with CAPA compared to COVID-19 patients without evidence for *Aspergillus*.[6,25] There was a trend towards lower mortality in CAPA patients receiving antifungal therapy, compared with untreated cases, which suggests that the mortality, at least in part, may be attributable to IA.[6,25] To gain more insight into the pathophysiology of CAPA, it is critical to perform histopathological examination of lung tissue samples. However, similar to bronchoscopy, there is strong consensus in the literature that autopsy and thoracic surgery procedures classify as aerosol-generating procedures,[26] and as a consequence, the number of proven CAPA cases is still very limited. Indeed, our literature review indicated that only in 7 of 175 (4%) CAPA cases the infection was proven, including the current case (Table S1). All classification of proven cases relies on the demonstration of invasive growth of septate hyphae, and the criteria are similar in the various definitions of IA.[27-29] Serum GM was performed in six proven cases, but found negative in four, which underscores the limited diagnostic value of this biomarker. Serum beta-D-glucan (BDG) might be a more sensitive marker as it was found to be positive in a higher proportion of patients.[15] However, this marker is not specific for IA and might be detected in patients with candidiasis and *Pneumocystis* pneumonia.

Various CAPA classification criteria have been used mostly based on those recommended for diagnosing IA in the ICU [28] or those proposed for patients with influenza-associated pulmonary aspergillosis.[27] The various definitions hamper international CAPA surveillance studies and comparability of studies. The recently published ECMM/ISHAM CAPA consensus definitions might help to further standardise research in this area and support uniform patient classification.[30] Clearly, the utility of certain diagnostic procedures, such as non-directed bronchial lavage (NBL), and the performance of diagnostic biomarkers on non-validated samples such as tracheal aspirate and NBL remain to be determined. The difficulty in diagnosing CAPA and the associated risks of diagnostic procedures complicates patient management. A recently published management algorithm recommends to consider a diagnostic fungal work-up in COVID-19 patients in the ICU who have a positive aspergillus test performed on upper respiratory tract specimens, such as sputum or tracheal aspirates, and in those who show clinical deterioration or persistent poor respiratory function with no other explanation, or

progressive radiology.[31] When the diagnosis of CAPA is confirmed initiation of antifungal therapy should be considered following international treatment guidelines, which recommend triazoles, such as voriconazole or isavuconazole, as first-line treatment.[23,32] In our case, despite voriconazole therapy, the patient died due to concomitant involvement with coronavirus and failure to antifungal therapy. In *A fumigatus*, triazole resistance should be considered in azole-treatment failure, but in our case, *A flavus* was recovered, which is the predominant *Aspergillus* species causing aspergillosis in Iran.[17,33,34]

In conclusion, recovery of *Aspergillus* species in a critically-ill COVID-19 patient should not be ignored, but requires a diagnostic workup despite suboptimal performance of relevant biomarkers. The new consensus definitions and reporting of proven CAPA cases will help to further understand the pathophysiology of IA in patients with COVID-19 and help to optimise clinical management.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Mohamad Salehi: Investigation (equal); Project administration (equal); Writing-review & editing (equal). **Nasim Khajavirad:** Methodology (equal); Writing-original draft (equal). **Arash Seifi:** Investigation (equal); Methodology (equal). **Faeze Salahshour:** Investigation (equal); Methodology (equal). **Behnaz Jahanbin:** Investigation (equal); Methodology (equal). **Hossein Kazemizadeh:** Investigation (equal). **jamal Hashemi:** Methodology (equal); Validation (equal). **Seyed Ali Dehghan Manshadi:** Investigation (equal); Methodology (equal). **Mohammad Kord:** Software (equal); Writing-original draft (equal). **Paul E. Verweij:** Writing-original draft (equal). **sadegh Khodavaisy:** Data curation (equal); Methodology (equal); Project administration (equal); Writing-original draft (equal); Writing-review & editing (equal).

AUTHOR CONTRIBUTIONS

MRS, NK, FS, HK, AS, SJH, SADM and MK conceived the study, treatment, and discussed the case and the implications; S.KH., MK and BJ diagnosed the case; S.KH., MRS and PEV wrote the manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the analysis.

ORCID

Mohammadreza Salehi https://orcid.org/0000-0002-1987-5929
Arash Seifi https://orcid.org/0000-0002-6174-0315
Seyed Ali Dehghan Manshadi https://orcid.org/0000-0002-0619-2950
Paul E. Verweij https://orcid.org/0000-0002-8600-9860
Sadegh Khodavaisy https://orcid.org/0000-0001-8039-4991

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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